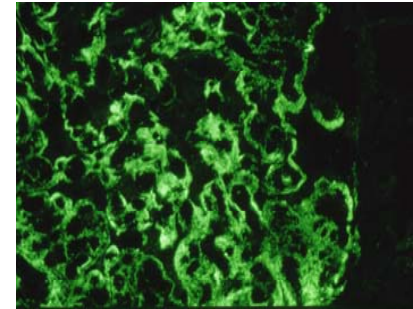
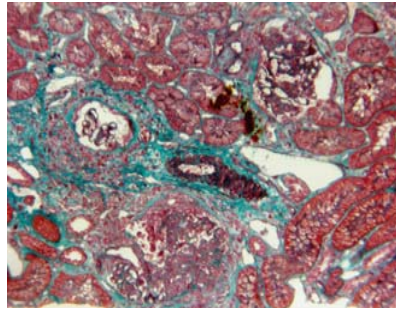


TREATMENT OF LN: WHAT'S UP DOC?

Fadi Fakhouri, Hôpital Necker, Paris

LN TREATMENT

LN class IVG
NS SCr 90 $\mu\text{mol/l}$



Induction TRT

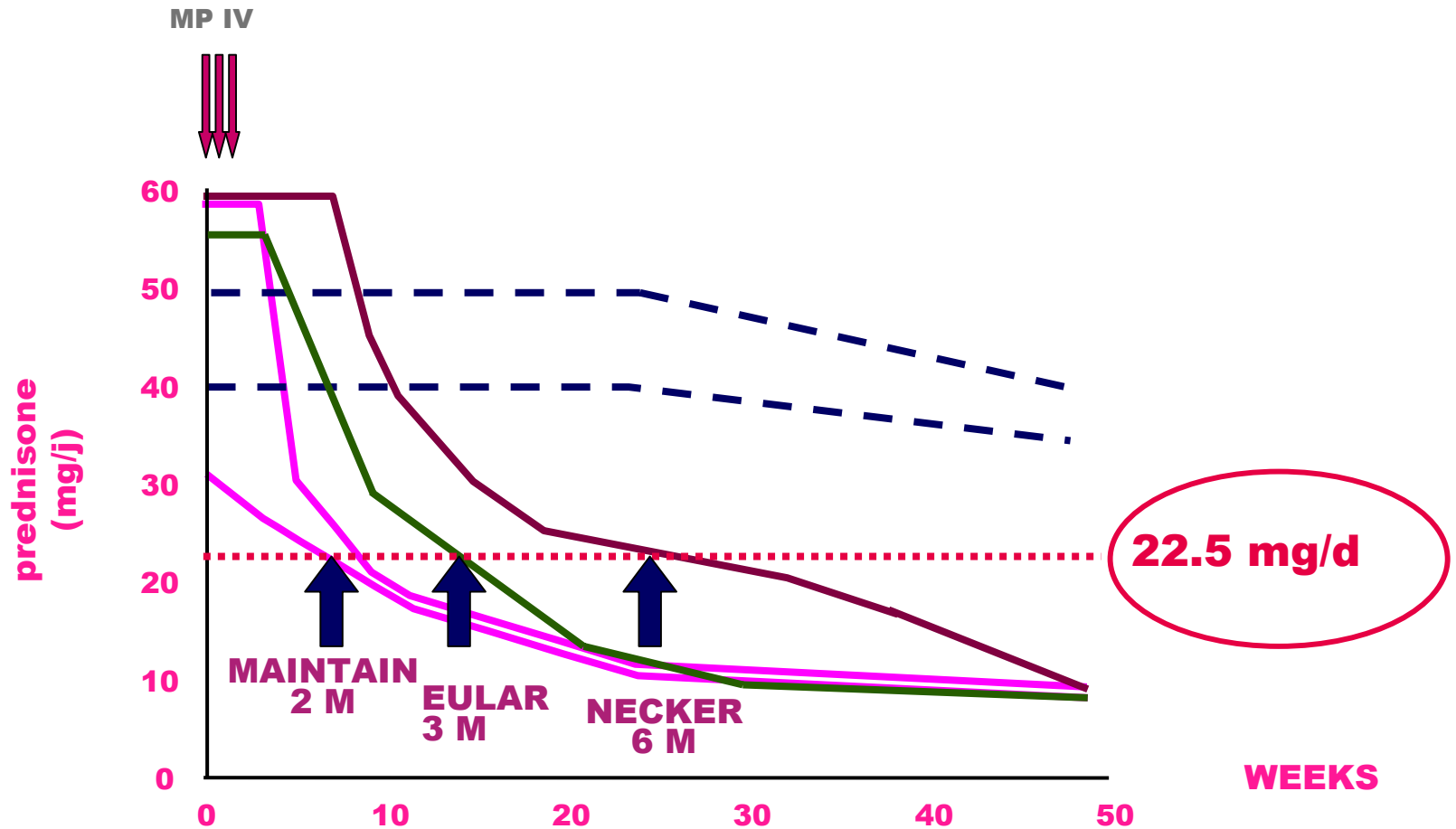
Maintenance TRT

STEROIDS



LN TREATMENT

STERIODS : a great uncertainty



LN TREATMENT

Induction TRT

Maintenance TRT

STEROIDS

0.75-1 mg/kg/d

0.5 mg/kg/d

0.25 mg/kg/d

M1

M3

M6



LN TREATMENT

Induction TRT

Maintenance TRT

STEROIDS

0.75-1 mg/kg/d

0.5 mg/kg/d

0.25 mg/kg/d

M1

M3

M6



Cardiovascular risk / statin / ACEI
Osteoporosis, etc.

LN TREATMENT

Induction TRT
STERIODS

Maintenance TRT

0.75-1 mg/kg/d

0.5 mg/kg/d

0.25 mg/kg/d

M1

M3

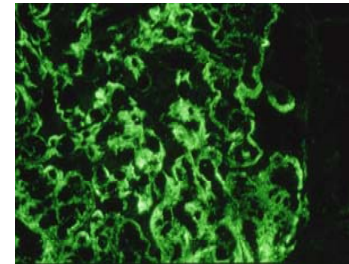
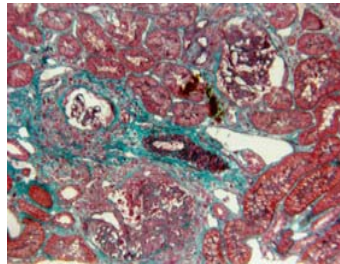
M6



If LN relapses, change your IS

LN TREATMENT

LN class IVG



Induction TRT

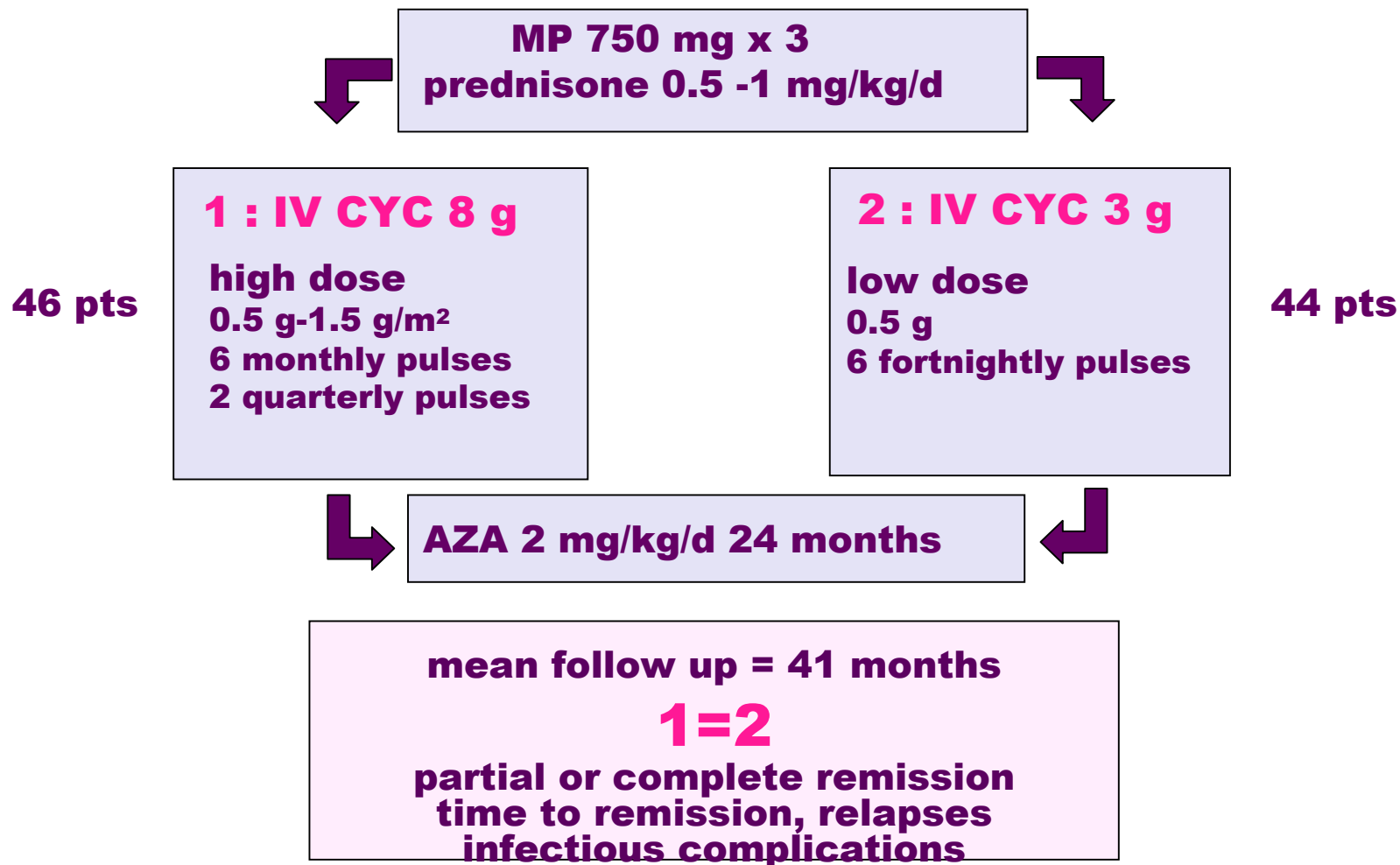
Maintenance TRT

STEROIDS

EURO-LUPUS CYP



The Euro-Lupus Nephritis Trial



The Euro-Lupus Nephritis Trial

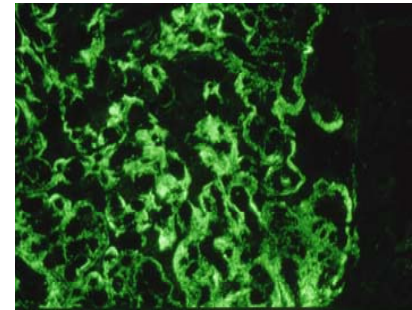
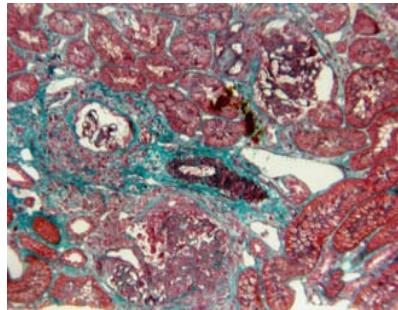
- **proliferative LN**

class III	25%
class IV	67%
class Vc, Vd	8%
- **70% caucasians**
- **SCr 110±6 mmol/l**
- **only 8% had previous IS therapy**

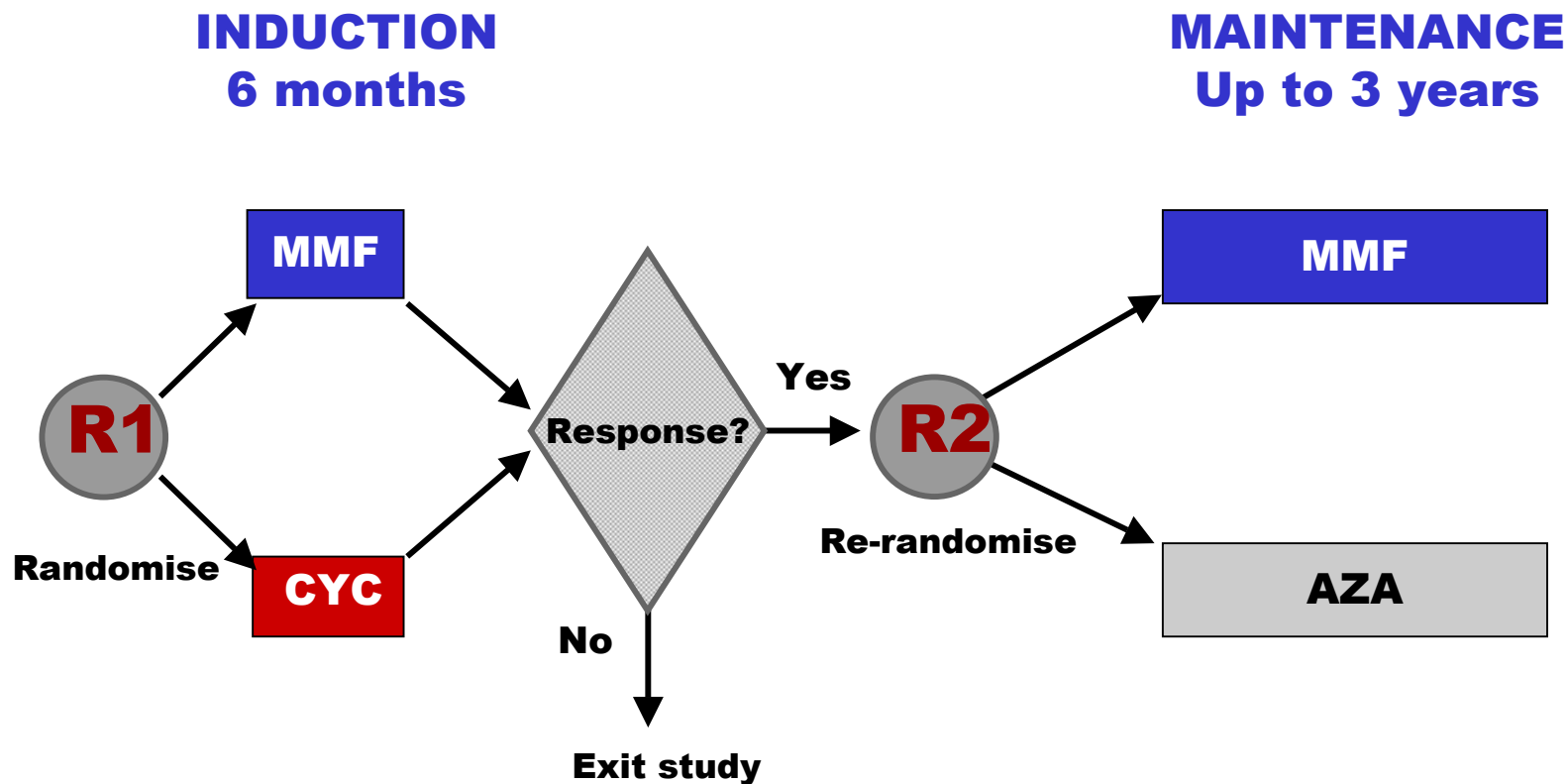
LN TREATMENT

WHY NOT MMF?

LN class IVG



Aspreva Lupus management study (ALMS)



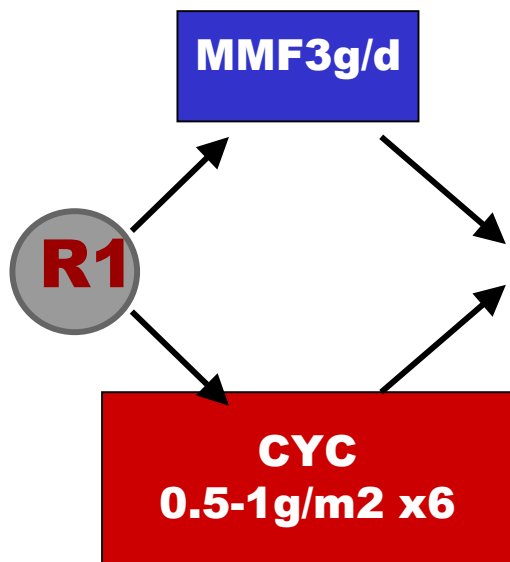
Aspreva Lupus management study (ALMS)

Primary hypothesis : MMF > CYP

LN III, IV, V

INDUCTION
6 months

N 370
39.7% White
33.2% Asians
27% others



Response :
“decrease in Puria and
improvement/stabilisati
on of SCr”

Aspreva Lupus management study (ALMS)

Primary hypothesis : MMF > CYP

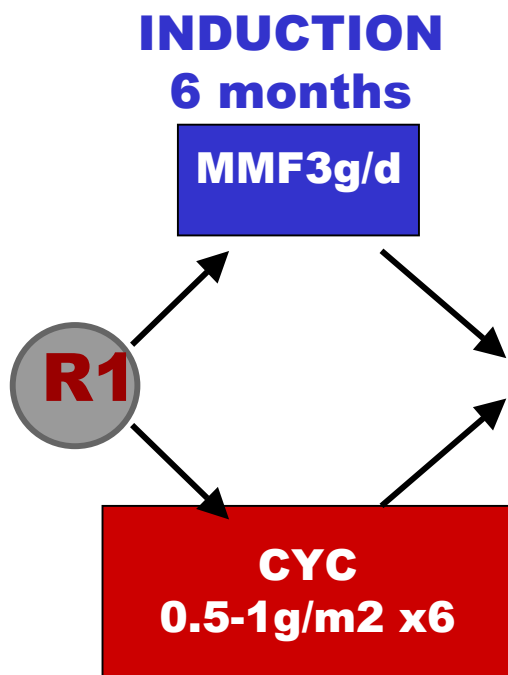
LN III, IV, V

N 370

39.7% White

33.2% Asians

27% others



Response :
“decrease in Puria and
improvement/stabilisati
on of SCr”

Response 6M

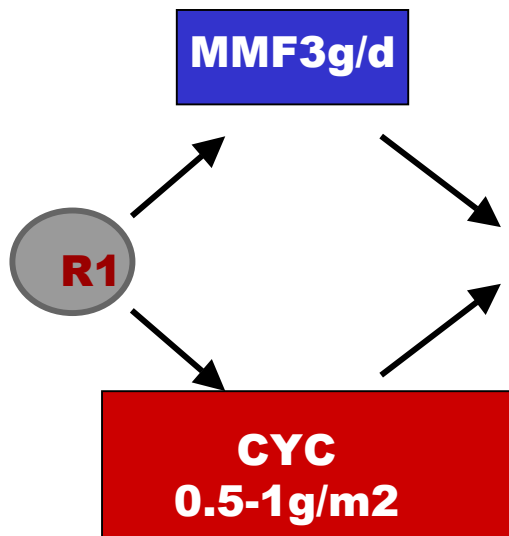
MMF 56.2%

CYP 53%

Aspreva Lupus management study (ALMS)

INDUCTION
6 months

N 370
39.7% w
33.2% A
27% others



Response :
“decrease in Puria and
improvement/stabilisation of
SCr”

Response
MMF 56.2%
CYP 53%

Others

MMF 60.4%
CYP 38.5%

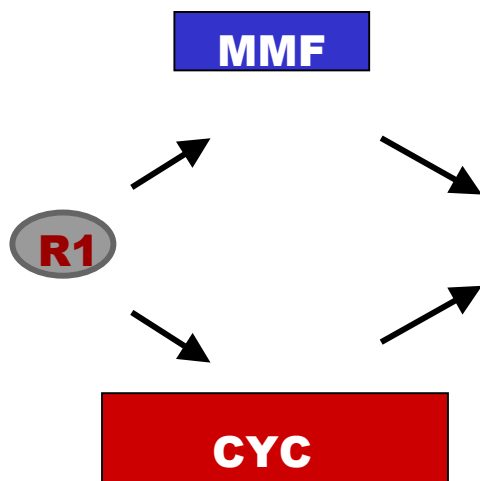
Hispanic

MMF 60.9%
CYP 38.8%

Aspreva Lupus management study (ALMS)

INDUCTION

6 months



N 370

39.7% w

33.2% A

27% others

Response :
“decrease in Puria and
improvement/stabilisation
of SCr

MMF 56.2%

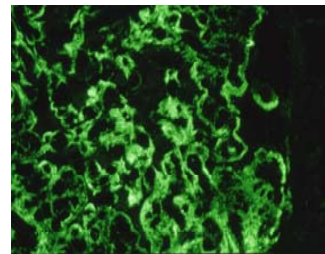
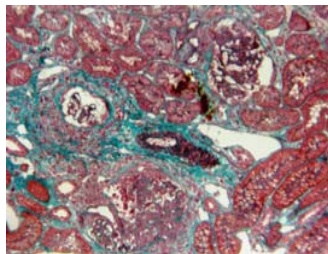
CYP 53%

Nb SAE+ Infections + deaths with MMF > CYP

LN TREATMENT



LN class IVG



Induction TRT

Maintenance TRT

STERIODS



CR



Maintenance TRT

EURO-LUPUS CYP



No remission

2nd EURO-LUPUS
MMF
RTX



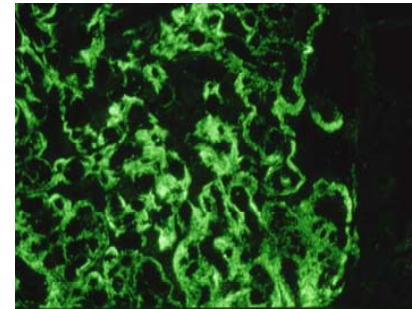
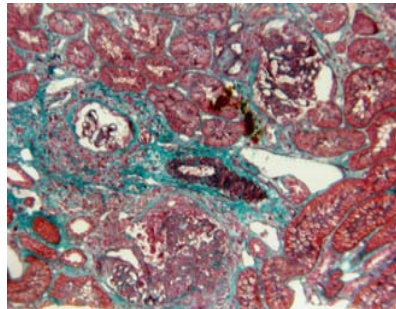
Relapse

LN TREATMENT

Rituximab?!!

What's this stuff Dr Fadouki?

LN class IVG



RTX in LN

Retrospective study (7 centers in Paris)

Inclusion criteria

SLE

Active LN III, IV or V

Follow-up > 12 months

Partial remission

Decrease in Puria > 50%

Stabilisation of GFR

Complete remission

Puria < 0.5g/d

Huria \geq 25 RBC/ μ L

Normalisation or increase > 50% of GFR

Histological remission

B cell depletion

CD19+ < 5/mm³ (and <1%)

Courtesy of C. Melander

RTX in LN

17 pts (10/2003 - 12/2006)

16 F, median age 24 y (17-37)

7 Afr/Ant

NS 15/17

GFR < 60 mL/min 6

HD 2

RPGN 3

LN IV (6), IV + V (6), V (5)

Follow-up

23 mois (12-51 mois)

RTX in LN

RTX 375mg/m² * 4 (n=13)

Maintenance RTX entretien (n=8)

Cs

MP (n=12)

P.o. (n=16)

Associated TRTS

CYP (n=3)

MMF (n=2)

HCCQ (n=5)

ACEI (n=13)

RTX in LN: Side effects

Infections (n=5)

Neutropenia (n=4)

Immediate reactions (n=3)

2 deaths

Acute RV failure

Intracerebral bleeding

PRES (n=2)

Thrombosis (n=2)

RTX in LN: Renal outcome

	Classe IV (n=12)	Classe V (n=5)	All (n=17)
PR	2	0	2
CR	5	2	7
NR	1	3 (1†)	4 (1†)
HD	4	0	4

RTX in LN: Renal outcome

	Classe IV (n=12)	Classe V (n=5)	All (n=17)
PR	2	0	2 \uparrow
CR	5	2	7 \downarrow
NR	1	3 (1†)	4 (1†)
HD	4	0	4

Delayed response (>6 Months): 5/9

RTX in LN

Predictors of renal response

	Remission (n=9)	No remission (n=8)	p
African	1	6	0.02
RPGN	0	3	0.08#
B cell depletion M1	8/8	1/6	0.003
Duration of B depletion (M)	23	4	0.01

ACR, Shirish, 2007

RTX in LN

Predictors of B cell depletion M1

	B depletion (n=12)	No B depletion (n=5)	p
African	2/12	4/5	0.02 *
Puria (g/d)	4.6	6.6	NS
Alb (g/L)	28	18	0,01
Resistance to conventional TRT	4	5	0.03
HACA	0/6	2/3	NS *

**Looney, 2004*

The « quality » of B cell depletion: a major issue in SLE

B cell depletion depends on

Ethnicity

Anti-RTX Ab

RTX serum level

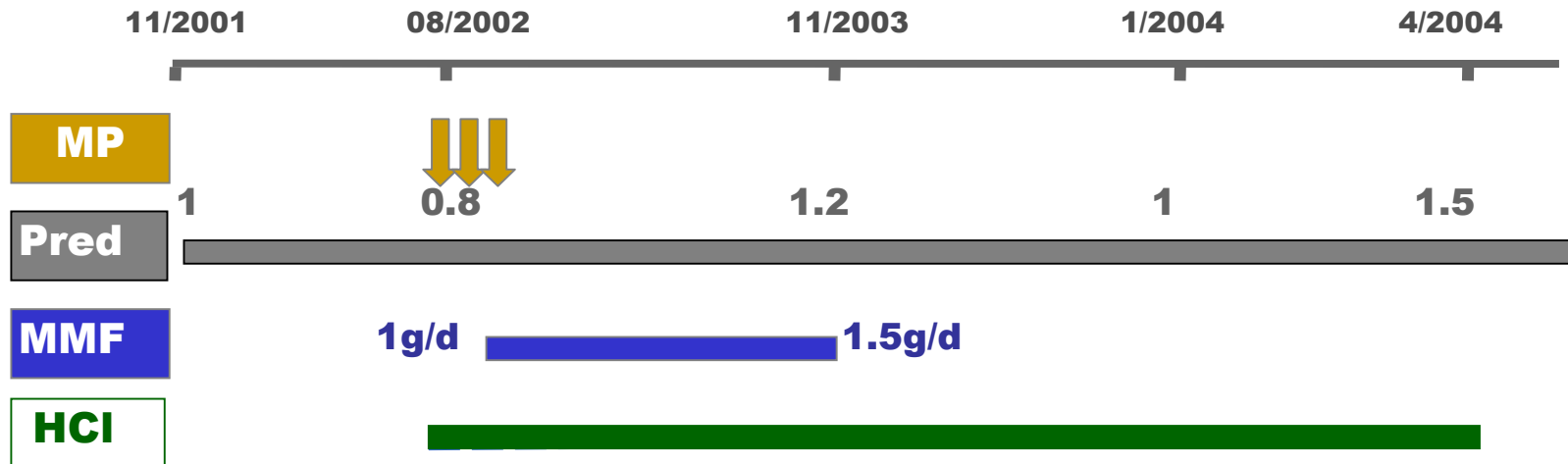
Fc γ RIIIa

HypoC3

HypoAlb

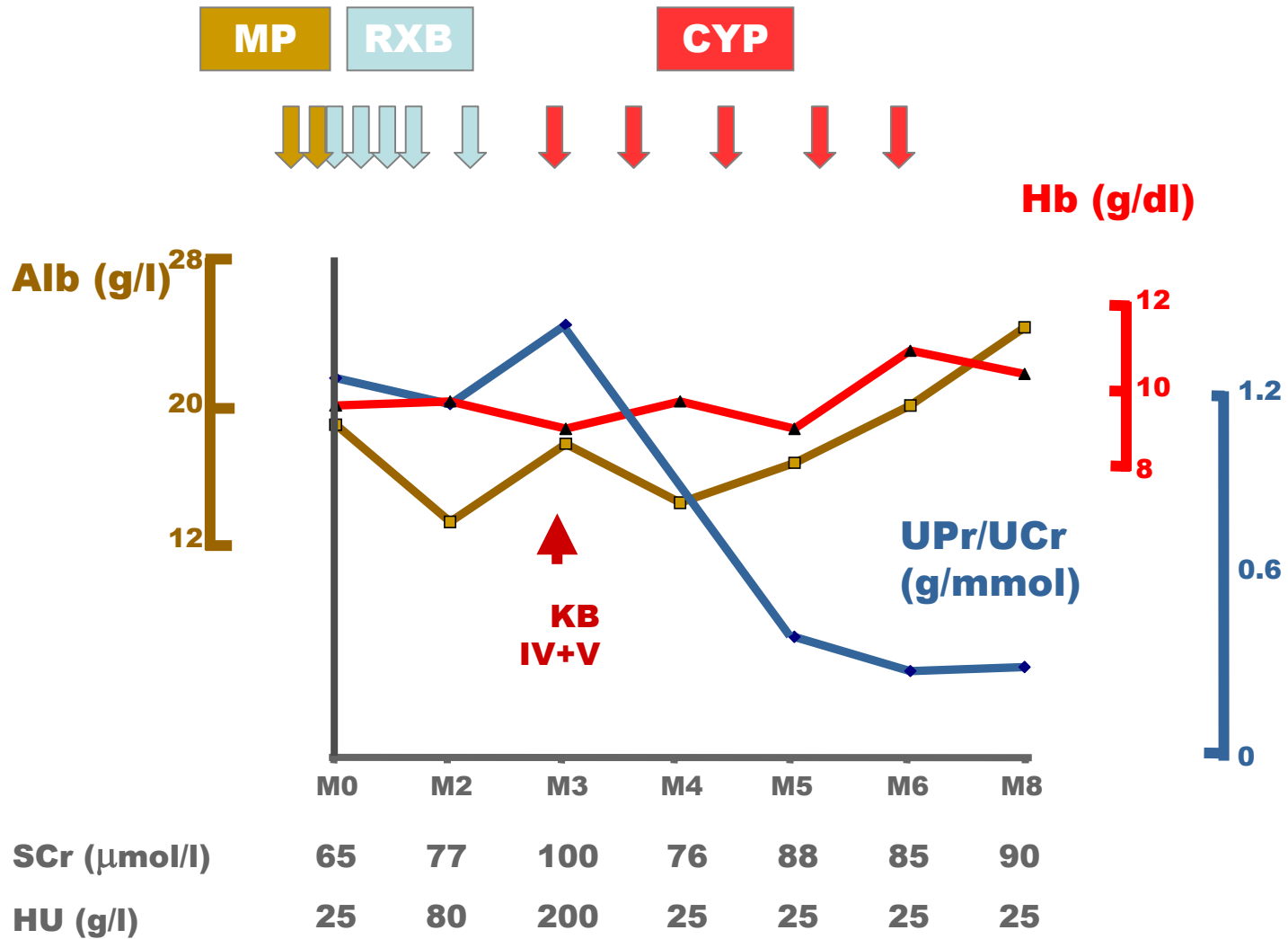
rituximab and LN

- Skin vasculitis
- arthritis
- **classe V**
- périocarditis
- pleuritis
- périocardite
- septicemia pneumo
- fever
- pleuritis
- Skin vasculitis

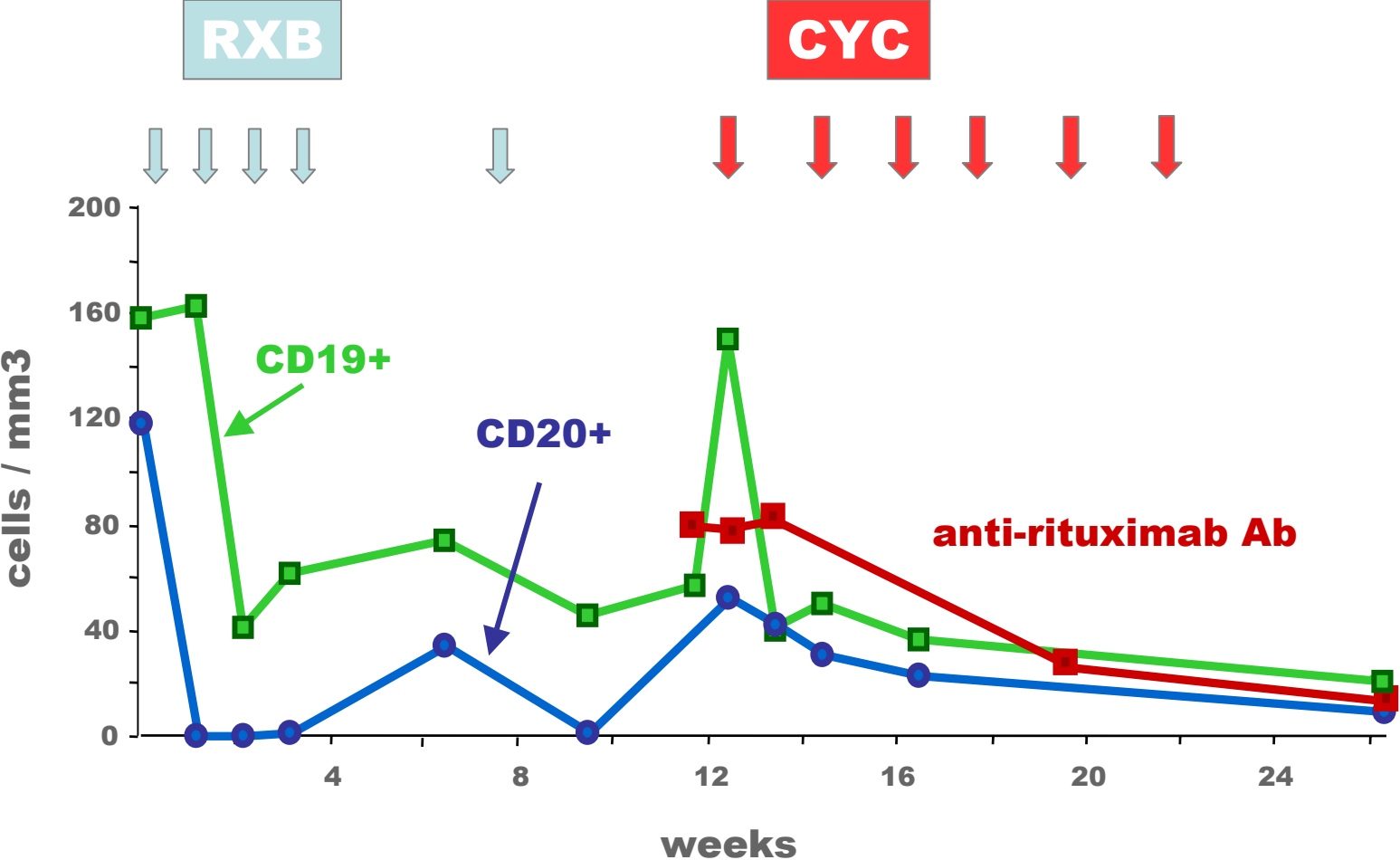


SCr ($\mu\text{mol/l}$)	65	67	66	65
Pu (g/d)	2.6	10.8	10.9	5.24
Hu	+	+	+	++
Hb (g/dl)	11.3	11.3	10.9	9.5
Alb (g/l)	25	20	21	17

rituximab and LN



rituximab and LN



RTX in LN: What about CS?

	Initial CS (mg/kg/d)	Last CS (mg/kg/d)	p
All (n=17)	0.7 (± 0.4)	0.2 (± 0.1)	<0.001
Responders (n=9)	0.7 (± 0.4)	0.1 (± 0.07)	0.003
Non responders (n=4)	0.7 (± 0.5)	0.3 (± 0.2)	0.1
HD (n=4)	0.7 (± 0.3)	0.1 (± 0.06)	0.04

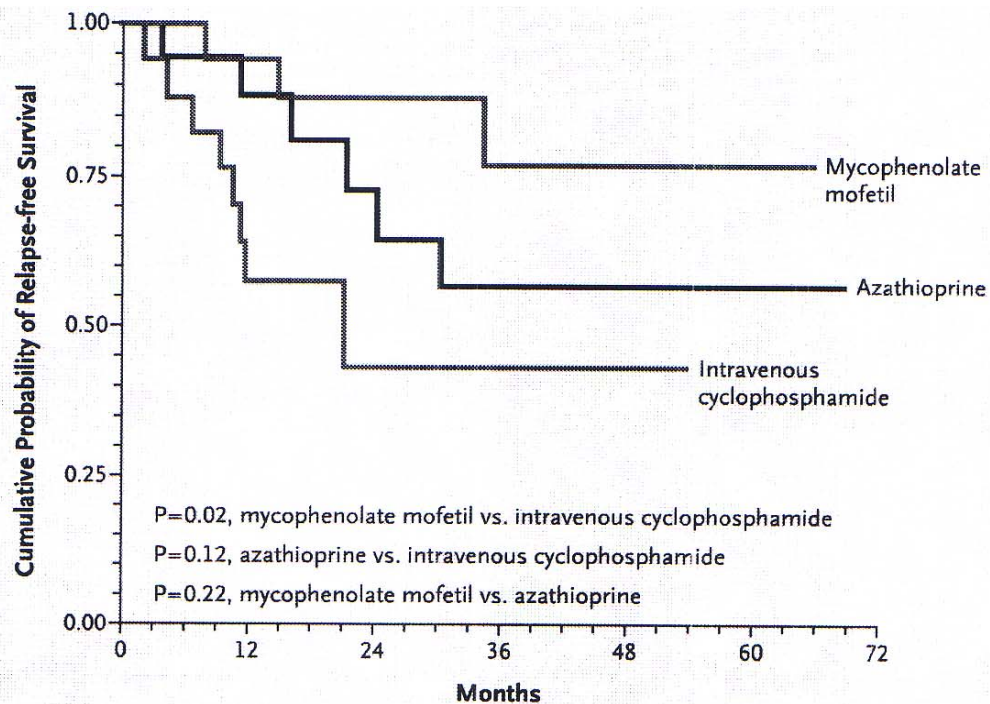
RTX in LN

African
RPGN = High risk of RTX failure

If no B cell depletion at M1...

change your IS

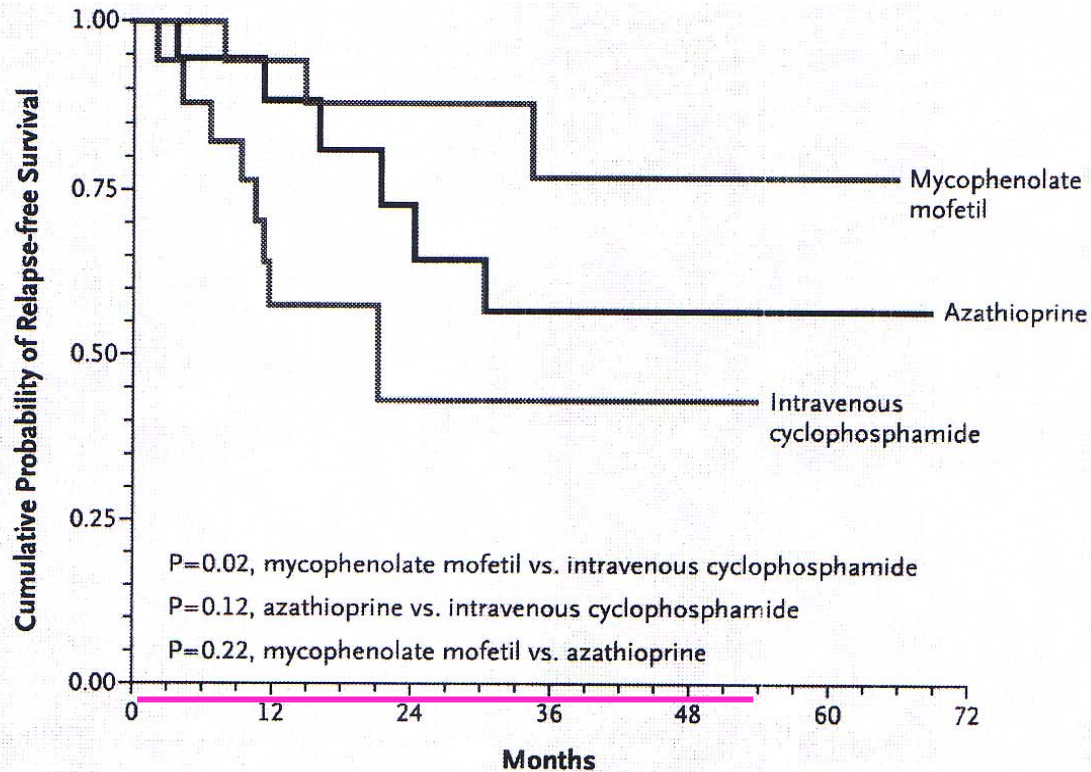
LN: Maintenance TRT



No. at Risk

Azathioprine	19	15	10	6	4	3	1
Intravenous cyclophosphamide	17	10	4	2	2	1	1
Mycophenolate mofetil	19	17	12	8	3	2	1

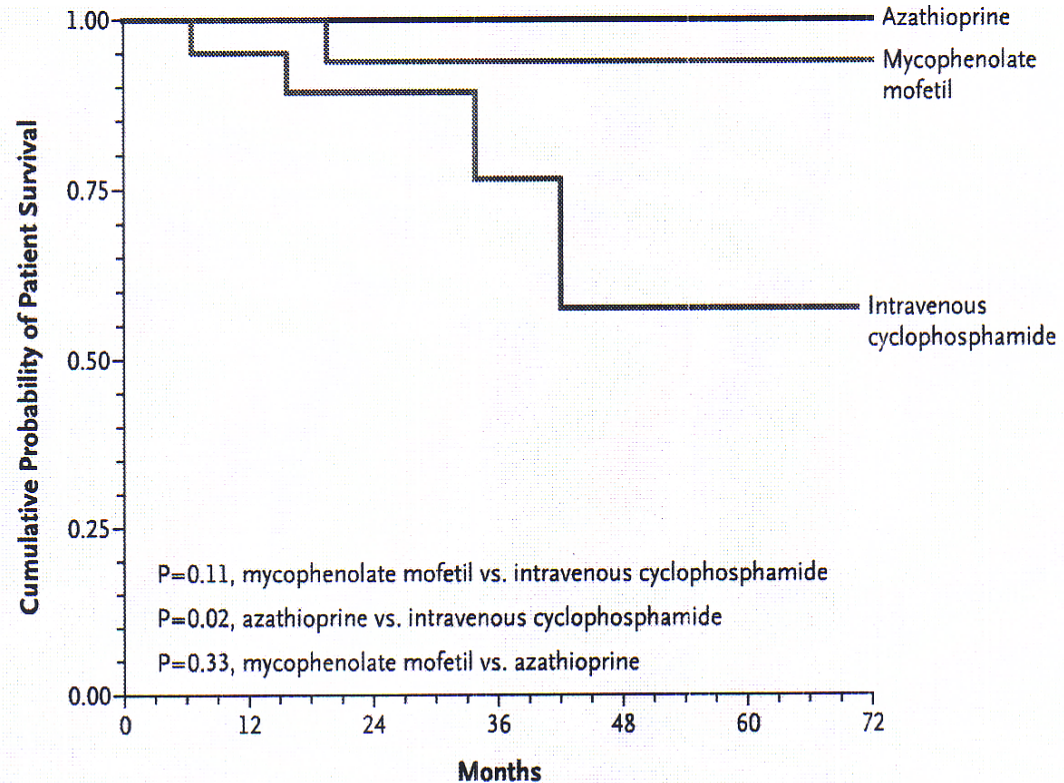
LN: Maintenance TRT



No. at Risk

Azathioprine	19	15	10	6	4	3	1
Intravenous cyclophosphamide	17	10	4	2	2	1	1
Mycophenolate mofetil	19	17	12	8	3	2	1

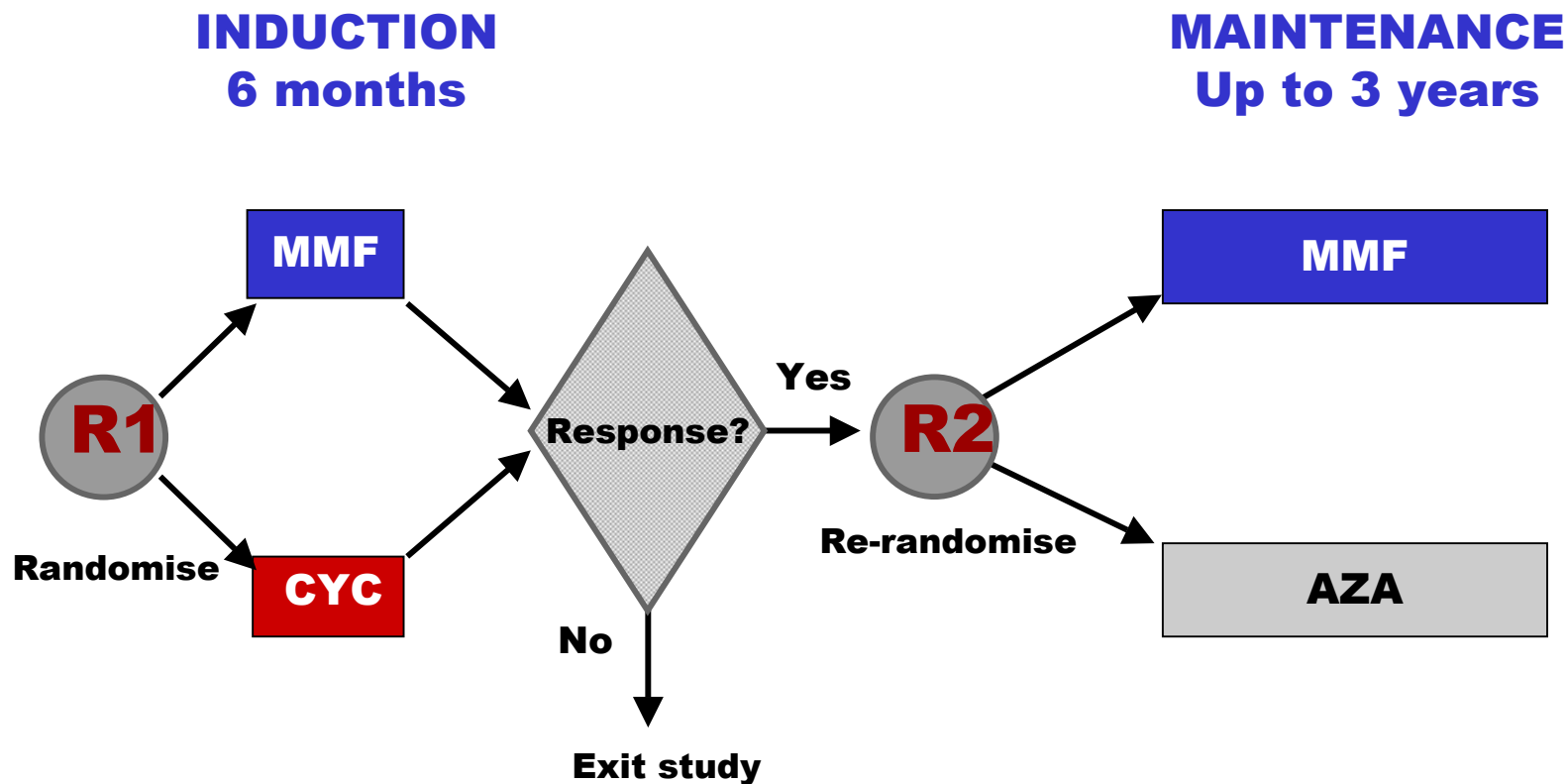
LN: Maintenance TRT



No. at Risk

Azathioprine	19	19	15	10	9	4	2
Intravenous cyclophosphamide	20	19	12	6	3	2	1
Mycophenolate mofetil	20	20	14	11	6	2	2

Aspreva Lupus management study (ALMS)

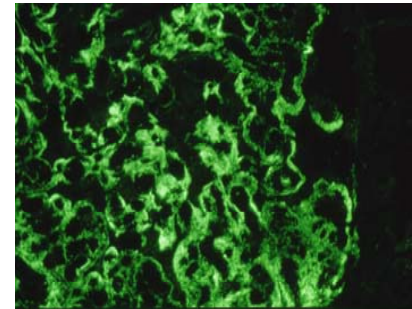
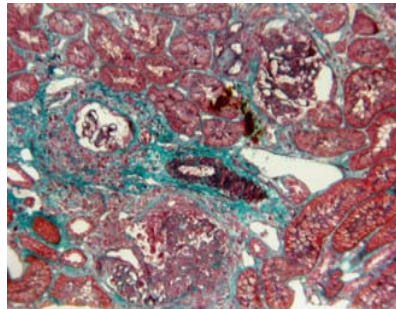


LN TREATMENT

Pharmakocinetics?!!

Is it really necessary Dr Farouki?

LN class IVG



PK study of MMF in patients with SLE and design of bayesian estimator using limited sampling strategies.

Zahr N et al. Clin Pharmacokinet. 2008

« A large interindividual variability in MPA PK »

Max plasma concentration	13.6 \oplus 8.4 mg/mL
Trough plasma concentration	1.4 \oplus 1.2 mg/mL
Time max plasma concentration	1.1 \oplus 1.2 mg/mL
AUC12	32.2 \oplus 17.1 mg/mL

PK of MMF in patients with AID compared to RT recipients

Neumann I, J Am Soc Nephrol. 2003

	AID	RT	
Cmax MPA (mg/L)	21.8 \oplus 14.09	36.8 \oplus 18.02	0.017
C12h MPA (mg/L)	4.1 \oplus 3.27	1.8 \oplus 1.15	
0.018			

Therapeutic drug monitoring of mycophenolic acid in solid organ transplant patients treated with MMF: review of the literature.

Arns et al. Transplantation 2006

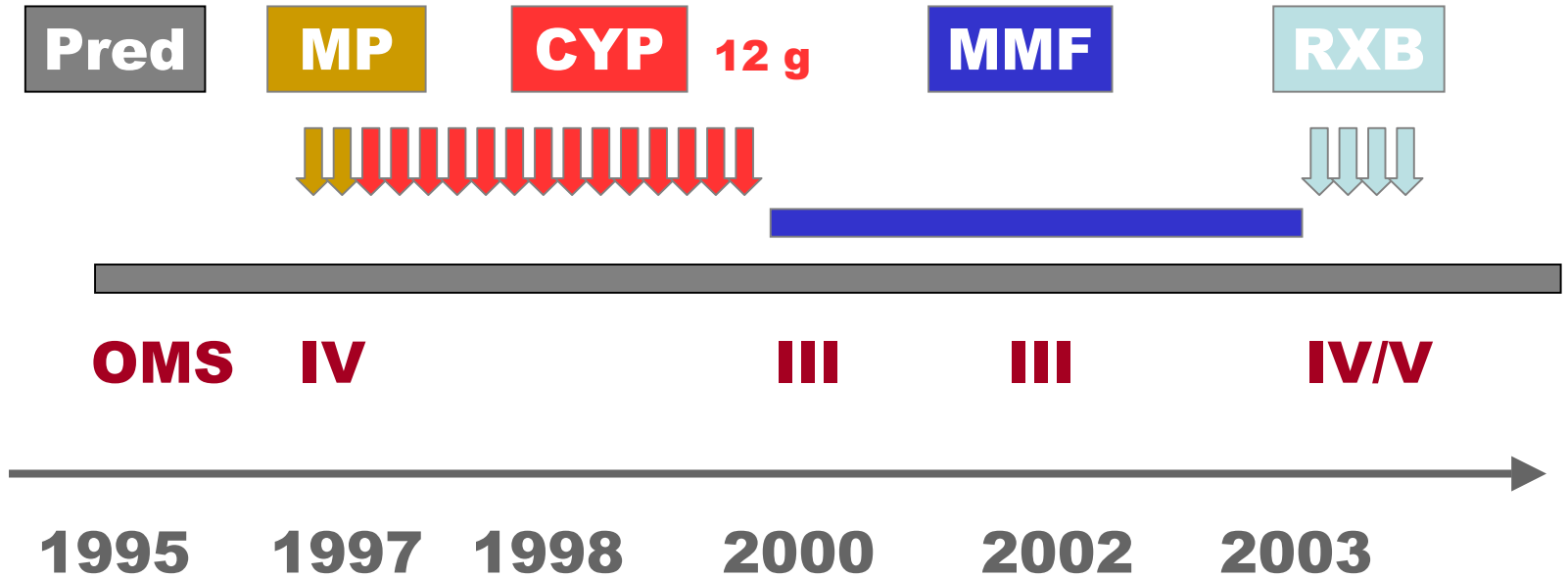
« The current review of the literature indicates no clear support for a substantial clinical benefit of TDM and more data from prospective randomized trials are needed »

PK of MMF in SLE

What is the optimal MMF PK in SLE?

Does PK impact long-term LN outcome?

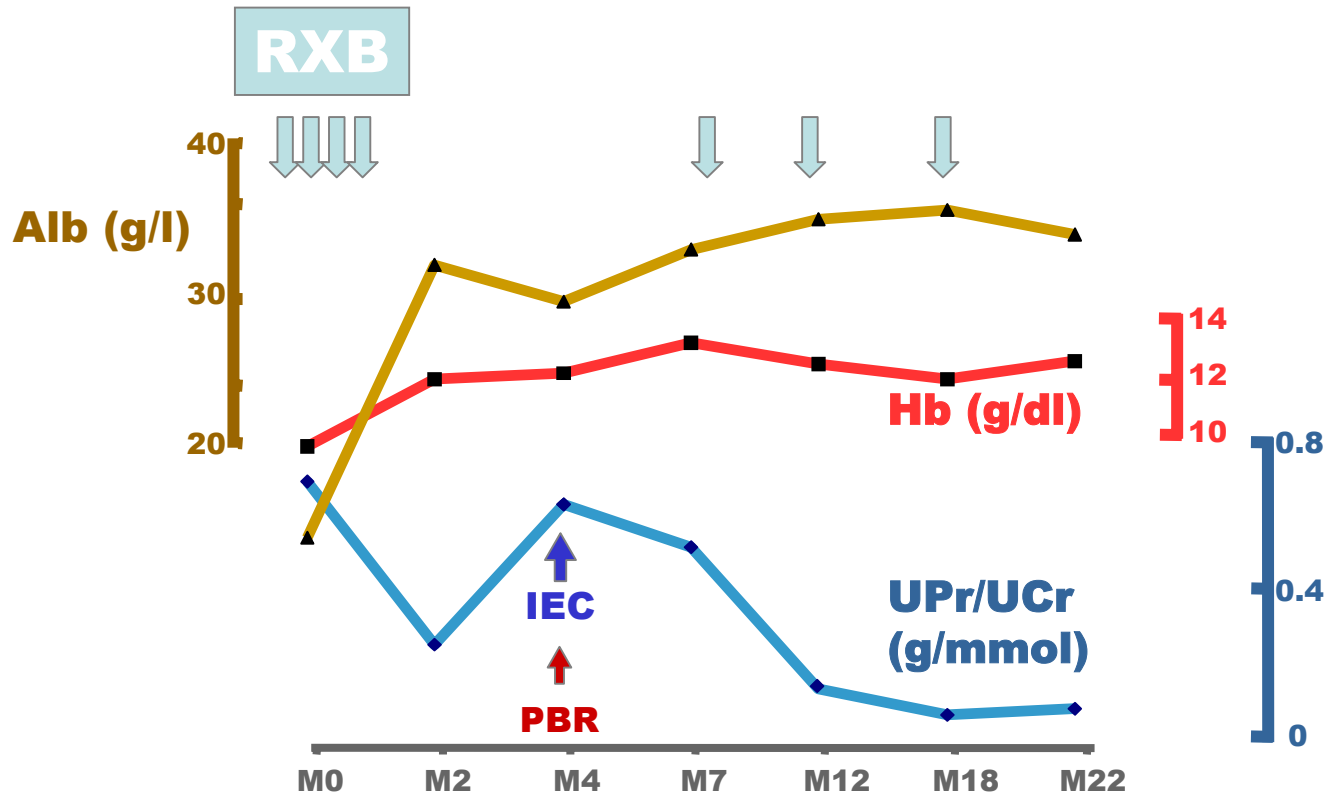
RTX as a maintenance TRT in NL



PCr ($\mu\text{mol/l}$)	89	63	70	82	137
Pu (g/d)	12.5	0	1.8	4	7

Relapse after remission

rituximab in LN : case 1



SCr (□ mol/l)

Hu (GR/ml)

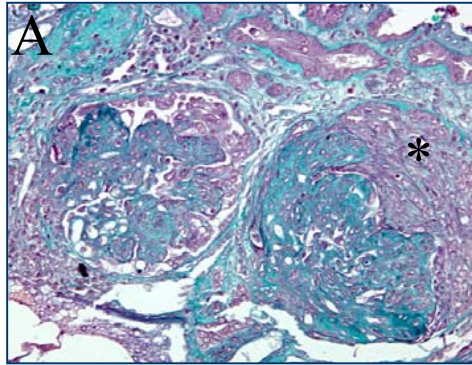
aDNA (%)

CD19⁺ (%)

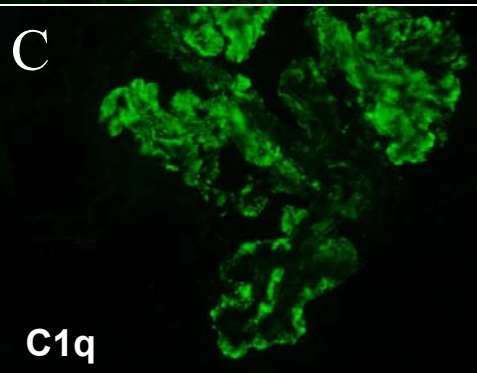
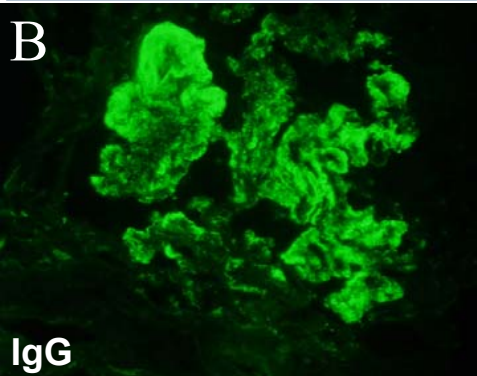
Ig (g/l)

137		113		110		90
200	200	200	25	25	0	0
36		14		12		13
20	0.02	0.06	0.4	1.7	2.9	0.05
3.4			3			5.8

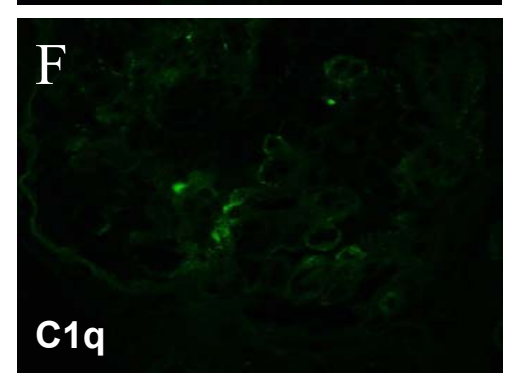
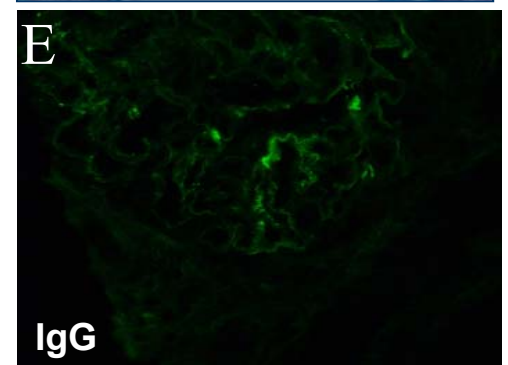
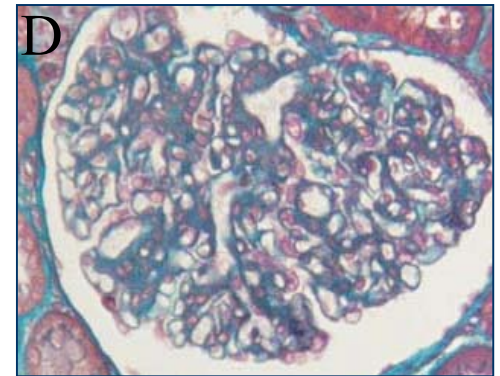
rituximab in LN: case 1



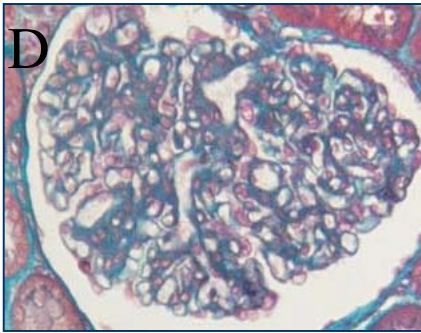
Before RTX



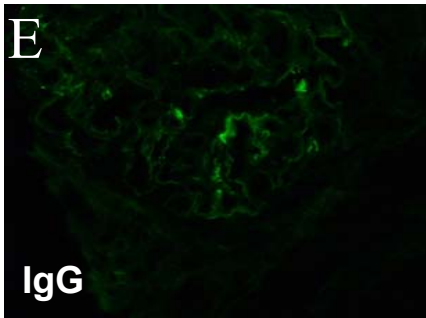
After RTX



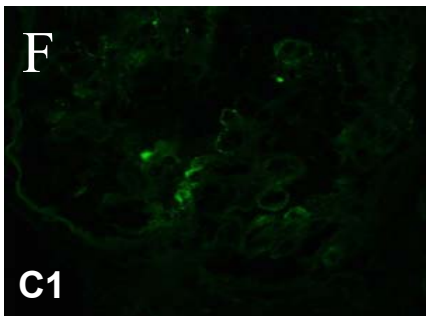
rituximab in LN: case 1



RTX induction / maintenance treatment



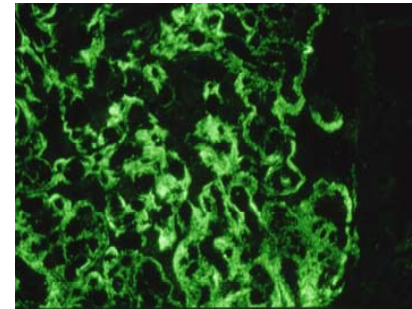
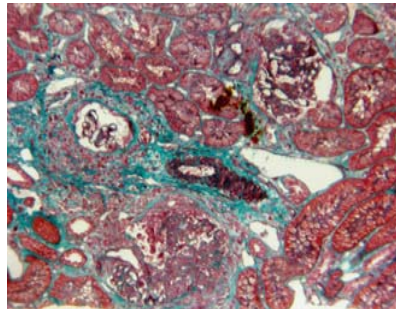
4.5 year-Fup
Off steroids
ANA Negative



LN TREATMENT

Another pill Fadi?

LN class IVG



Hydroxychloroquine: A magic pill in SLE?

Antithrombotic

Effect on lipids

Marker of SLE flares

Reduces mortality

Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L).

Alarcon GS, Ann Rheum Dis. 2007

Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis.

Kasinton N, Lupus. 2006

Low blood concentration of FCQ is a marker for and predictor of disease exacerbations in patients with SLE

Castedoat-Chalumeau, AR 2006



QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

120

23

106

14

A randomized study of the effect of withdrawing HCQ sulfate in SLE.

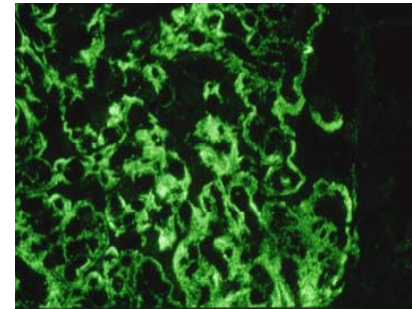
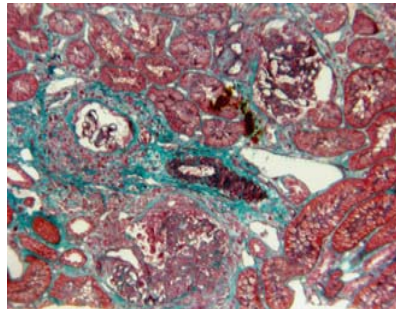
The Canadian Hydroxychloroquine Study Group NEJM 1991

		Flare-up
N= 47 SLE HCQ+ (270 mg/j)	N=25 HCQ+	9/25
	N=22 HCQ-	16/22

LN TREATMENT

Are you sure darling?

LN class IVG



Low blood concentration of FCQ is a marker for and predictor of disease exacerbations in patients with SLE

Castedoat-Chalumeau, AR 2006



QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

SLE Flares
Arthritis 9
Skin 4
Alopecia 3
LN 1

120

23

106

14

A randomized study of the effect of withdrawing HCQ sulfate in SLE.

The Canadian Hydroxychloroquine Study Group NEJM 1991

		Flare-up	
N= 47 SLE HCQ+ (270 mg/j)	N=25 HCQ+	9/25	Flares-up in 25 pts 61 manifestations Skin 24 Mucosal ulcers 13 Arthritis 13
	N=22 HCQ-	16/22	Constitutional signs 11 LN 0

LN TREATMENT

What to keep in mind?

Less CS

Euro-Lupus

RTX

PK

HCQ

LN TREATMENT

What to keep in mind?

Less CS

Euro-Lupus

RTX

PK / HCQ

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.